Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 4, pp. 1105–1112, 2010

Printed in the USA. 0360-3016

doi:10.1016/j.ijrobp.2009.06.042

CLINICAL INVESTIGATION **Breast**

LOCOREGIONAL OUTCOMES OF INFLAMMATORY BREAST CANCER PATIENTS TREATED WITH STANDARD FRACTIONATION RADIATION AND DAILY SKIN BOLUS IN THE TAXANE ERA

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Purpose: To assess locoregional outcomes of inflammatory breast cancer (IBC) patients who received standard fractionation radiation with daily skin bolus and taxanes as part of combined-modality therapy (CMT).
Methods and Materials: We retrospectively reviewed the charts of 107 patients diagnosed with IBC between January 1995 and March 2006 who presented to our department for adjuvant radiation therapy (RT).
Results: All patients received chemotherapy (95% anthracycline and 95% taxane), modified radical mastectomy, and RT to the chest wall and regional lymphatics using standard fractionation to 50 Gy and daily skin bolus. The RT to the chest wall was delivered via electrons (55%) or photons (45%) in daily fractions of 180 cGy (73%) or 200 cGy (27%). Scar boost was performed in 11%. A majority (84%) of patients completed the prescribed treatment. Median follow-up was 47 months (range, 10–134 months). Locoregional control (LRC) at 3 years and 5 years was 90% and 87%, respectively. Distant metastases–free survival (DMFS) at 3 years and 5 years was 61% and 47%, respectively.
Conclusions: Excellent locoregional control was observed in this population of IBC patients who received standard fractionation radiation with daily skin bolus and taxanes as part of combined-modality therapy. Distant metastases–free survival remains a significant therapeutic challenge.

Radiation, Inflammatory breast cancer, Combined modality treatment, Standard fractionation, Taxanes.

INTRODUCTION

Inflammatory breast cancer (IBC) is a unique entity compared to other non-inflammatory locally advanced breast cancers. The term ''inflammatory'' was first coined at Memorial Hospital by Lee and Tannenbaum in 1924 (1). Clinically IBC is diagnosed by erythema, edema, and induration developing in the breast over a rapid time course, and pathologically, widespread tumor emboli invading the dermal lymphatic system may be observed (2). The condition of IBC exhibits a tendency for early recurrence (3) and inferior prognosis (4, 5). Historically, outcomes with radiation and surgery alone were poor (6). Since the incorporation of neoadjuvant (NA) chemotherapy into treatment over the past several decades, a significant proportion of patients have demonstrated long-term survival (7).

Neoadjuvant chemotherapy in the management of IBC has been refined over the past decade. Anthracyclines have been shown to improve outcomes and are considered part of standard induction treatment for IBC (8, 9). The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial demonstrated that the addition of preoperative taxanes to anthracyclines improves response in operable breast cancer (10), and the Cancer and Leukemia Group B (CALGB) Trial 9741 showed that a dose-dense schedule of chemotherapy administration improves survival in breast cancer patients with node-positive disease (11). These studies have indirectly contributed to the incorporation of taxanes and dose-dense chemotherapy schedules into combined modality therapy (CMT) for IBC. Several studies have investigated the impact of these agents on survival outcomes in specific IBC populations (12–15).

When integrated with NA chemotherapy, both mastectomy and radiation therapy (RT) continue to have an important role in the locoregional management of IBC (16, 17). Given the rarity of the diagnosis, which represents fewer than 5% of newly diagnosed breast cancers (18), there are no randomized trials delineating optimal radiation regimens for this disease. Various single institutions have published

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Presented in part as a poster at the 50th Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Boston, MA, September 21–25, 2008.

Conflict of interest: none.

Received March 3, 2009, and in revised form June 12, 2009. Accepted for publication June 12, 2009.

their radiation techniques in patients receiving radiation as part of CMT (19–22), and 5-year locoregional control rates in these studies range from 78% to 92%. These studies, however, vary in sequencing of radiation (pre vs. post mastectomy), total dose (50–66 Gy), and fractionation schedules (once daily vs twice daily), making it challenging to draw definitive conclusions regarding radiation techniques. In addition, the use of taxanes, now common for IBC, was incorporated in only small proportions of the study populations, ranging from 4% to 40% (20–22). There is a paucity of data on the appropriate radiation regimen in an IBC population who largely receive taxane-containing regimens.

At our institution, over the past decade, IBC patients have been treated in a consistent fashion with anthracycline and taxane-containing chemotherapy, modified radical mastectomy (MRM), and locoregional radiation. This purpose of this study was to examine locoregional outcomes resulting from our technique using standard fractionation radiation to 50 Gy with daily skin bolus, a considerably lower radiation dose compared with other regimens recently reported. In addition, the use of daily skin bolus with no modification by skin reaction at our institution is considered aggressive. We therefore also aimed to assess toxicities and tolerability of this regimen among this specific population.

METHODS AND MATERIALS

Patient selection

The charts of patients diagnosed with IBC between January 1995 and March 2006 were retrospectively evaluated. Only patients irradiated in our department with curative intent were included. Patients with metastatic disease or disease recurrence before RT were excluded. Patients with a pathologic finding of tumor emboli invading the dermal lymphatics in their mastectomy specimen but who lacked clinical findings of IBC were excluded as well. Of 359 charts reviewed, 107 patients were identified who met these criteria, including 1 patient with synchronous bilateral IBC.

The majority of patients received their mastectomy and chemotherapy treatments at Memorial Sloan-Kettering Cancer Center (MSKCC). The diagnosis of IBC was made at the time of initial consultation, generally by an MSKCC surgeon or medical oncologist. Several patients were diagnosed and initially treated with chemotherapy and/or mastectomy at an outside institution before receiving radiation in our department. The diagnosis of IBC in these cases was made based on review of the patient's history, pathology findings, and outside physician documentation. All pathologic specimens were reviewed by the MSKCC pathology department confirming the diagnosis of invasive carcinoma. A skin biopsy (to assess the presence of tumor emboli in the dermal lymphatics) was performed in 65% of the study population.

Patient and tumor characteristics are listed in Table 1.

Table 1. Patient characteristics

Age (y)	50 (26–81)
Menopausal status	
Peri	7 (7%)
Pre	46 (43%)
Post	54 (50%)
Race/ethnicity	
African American	13 (12%)
Asian/Pacific Islander	4 (4%)
Caucasian	84 (79%)
Hispanic	3 (3%)
Other	3 (3%)
Skin punch biopsy	
Positive	55 (51%)
Negative	15 (14%)
Did not receive	37 (35%)
Hormone receptor status	
ER +	59 (55%)
PR +	36 (34%)
Her2 overexpression	40 (37%)
Her 2 status unknown	11 (10%)
Nodes positive (pathologic)	
0	23 (22%)
1–3	20 (19%)
4–9	37 (35%)
≥10	27 (25%)
Nodes evaluated	16 (0–49)
Nodal ratio	
>50%	37 (35%)
<50%	70 (65%)
Laterality	
Left	49 (46%)
Right	58 (54%)
Positive/close margins	13 (12%)
Margin status unknown	7 (7%)
Clinical response*	
At least partial response to chemotherapy	96 (90%)
Less than partial response	5 (5%)
Pathologic response*	
pCR in the axillary lymph nodes	23 (23%)
pCR in the breast	15 (15%)
2002 AJCC Stage (clinical)	
NX	6 (6%)
IIIB	94 (88%)
IIIC	7 (6%)

Abbreviation: pCR = pathologic complete response.

Characteristics are given as median (range) for continuous variables and *n* (%) for categorical variables.

* Includes only those patients who received NA chemotherapy.

Systemic therapies

The sequencing of chemotherapy, MRM, and RT is outlined in Fig. 1.

The majority of patients (95%) received anthracycline and taxane-containing chemotherapy. The various regimens administered are shown in Table 2. The AC-T regimen (doxorubicin (A) (60 mg/m^2) and cyclophosphamide (C) (600 mg/m^2) × 4 cycles, followed by paclitaxel (T) (175 mg/m^2) × 4 cycles) was most common. Before 2004, T was usually administered in the adjuvant setting after MRM, and after 2004, all of the chemotherapy, including T, was usually administered neoadjuvantly. Furthermore, after 2004, the majority of patients received neoadjuvant dose-dense (dd) chemotherapy, that is, AC-T chemotherapy delivered every 2 weeks rather than every 3 weeks. For the purpose of analysis, only patients who received all planned cycles of dd AC-T in the absence of other chemotherapeutic agents were classified as the ''dose-dense'' group.

Eleven patients received less common chemotherapy regimens categorized as ''other'' in Table 2. The regimens listed as ''other'' included: dd AC-T with gemcitabine; dd AC-T with gemcitabine and capecitabine; dd AC followed by weekly paclitaxel; dd AC followed by docetaxel; paclitaxel alone; docetaxel and cyclophosphamide; docetaxel followed by capecitabine; paclitaxel followed by cyclophosphamide, epirubicin, and 5-fluorouracil;

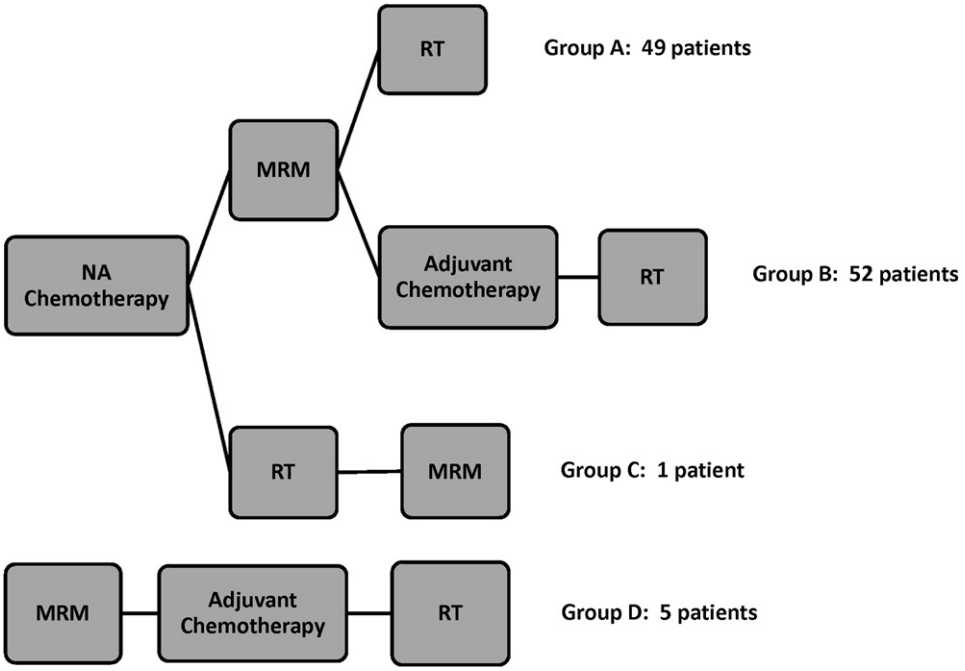

Fig. 1. Treatment groups.

cyclophosphamide, methotrexate, and 5-fluorouracil; carboplatin with paclitaxel. One patient with initially chemo-refractory disease received doxorubicin and vinorelbine, then vinblastine, cyclophosphamide, and doxorubicin, then gemcitabine, epirubicin, and docetaxel.

Clinical response to chemotherapy was documented by the medical oncologist and surgeon before mastectomy. The majority of patients achieved at least a partial response determined by clinical examination. Only 5 patients had less than a partial response (2 patients, no clear clinical evidence of response; 3 patients, local progression of clinical signs and symptoms during chemotherapy). No patient who developed distant metastases while undergoing chemotherapy was included in this study.

Table 2. Systemic treatment characteristics

Chemotherapy	
AC-T	71 (66%)
Q3 weeks	34 (32%)
Q2 weeks	37 (34%)
A-T-C	7 (7%)
TAC	6 (6%)
EC-T	5 (5%)
A-CMF	4 (4%)
CAF-T	3 (3%)
Other	11 (10%)
Hormonal therapy	
Tamoxifen only	13 (12%)
AI only	17 (16%)
Sequential tamoxifen + AI	22 (20%)
Other	7 (7%)
None	48 (45%)
Trastuzumab	13 (12%)

Abbreviations: AC-T = doxorubicin/cyclophosphamide followed by paclitaxel; A-CMF = doxorubicin followed by cyclophosphamide/methotrexate/5-fluorouracil; AI = aromatase inhibitor; A-T-C = doxorubicin followed by paclitaxel followed by cyclophosphamide; CAF-T = cyclophosphamide/doxorubicin/5-fluorouracil followed by paclitaxel; EC-T = epirubicin/cyclophosphamide followed by paclitaxel; TAC = docetaxel/doxorubicin/cyclophosphamide.

Surgery

All patients were treated with MRM. Of the patients, 94 (88%) had their surgeries performed at MSKCC. Six patients had immediate breast reconstruction, 3 of these at an outside institution. The 3 patients who received breast reconstruction at MSKCC had complete clinical response to chemotherapy documented by the surgeon at the time of the operation.

Pathologic complete response (pCR) in the breast indicated the absence of any tumor cells in the removed breast. We defined pCR in the axillary lymph nodes (pCR in the nodes) as no residual microscopic or macroscopic disease in the lymph nodes, independent of disease status of the breast. The percentages of patients achieving pCR are listed in Table 1.

Any patient who developed distant metastases or local progression after surgery and before RT was excluded.

Radiation technique for chest wall and regional lymphatics

The median time from surgery to RT was 137 days (range, 110–192 days) for the 57 patients who received adjuvant chemotherapy (Fig. 1, Groups B and D), and 50 days (range, 39–66) for the 50 patients who did not receive adjuvant chemotherapy (Fig. 1, Groups A and C).

Radiation therapy was delivered to an unreconstructed chest wall (CW) in 100 patients, to an intact (premastectomy) breast in 1 patient, and to a reconstructed breast in 6 patients. The target volume included the entire CW and the draining regional lymphatics. The median dose to the CW was 5040 cGy (range, 1080–5040 cGy). Skin bolus (0.5–1.0 cm) was applied daily to the entire CW to ensure adequate coverage of the skin by the prescription isodose line. Bolus remained on the skin for the entirety of RT. Boosting the

Table 3. Radiation therapy (RT) treatment characteristics of study patients

RT duration (days)	39 (34–64)
Regional lymphatic groups targeted	
Supraclavicular nodes	107 (100%)
Internal mammary nodes	65 (61%)
Axilla (posterior axillary boost)	29 (27%)
Scar boost performed	12 (11%)
Fraction size (cGy)	
180	78 (73%)
200	29 (27%)
Electrons/photons	
Electrons	59 (55%)
Photons	44 (41%)
Electrons + photons	4 (4%)

Characteristics are given as median (range) for continuous variables and *n* (%) for categorical variables.

mastectomy scar was not routinely performed. Radiation treatment characteristics are further detailed in Table 3.

The use of electrons rather than photons to treat the CW depended on patient anatomy, physician discretion, and available technology of the time, including the availability of CT-simulation, which became routine at MSKCC in April 1998. Our technique for post-mastectomy CT-based electron beam radiotherapy has been described in detail previously (23).

The electron-based CW technique always included the internal mammary nodes (IMNs) in the target volume. The IMNs were not always targeted in the photon-based CW technique, and their inclusion depended on the clinical judgment of the treating physician. When the IMNs were included in a photon CW plan, one of two techniques was used. Either a separate *en face* electron beam was added or, alternatively, the photon tangential fields were widened to incorporate the IMNs in the first four intercostal spaces.

Patients who experienced progression during RT were included in the analysis.

Statistical methods

Time to locoregional recurrence (LRR), distant failure, first failure, and overall survival (OS) were estimated using Kaplan-Meier methods. All times were estimated from the date of diagnosis, except for the analysis of response to neoadjuvant chemotherapy, which was estimated at the date of surgery, when pathologic response was assessed. For locoregional and distant failure, patients who died without a recurrence were censored at the time of death, and patients who were alive and free of each specific recurrence were censored at last follow-up. Cox proportional hazards regression was used to assess associations between time to LRR and various clinical and treatment characteristics. Fisher's exact test was used to assess relationships among these characteristics.

RESULTS

Survival analysis

The median follow-up for survivors was 3.8 years (range, 1.2–11.0 years). Results are shown in Figs. 2 to 5. Four patients had disease progression while undergoing radiation (2 local, 2 distant). Patients who failed during the course of RT were included in the survival analysis and were censored at the time of first failure or death.

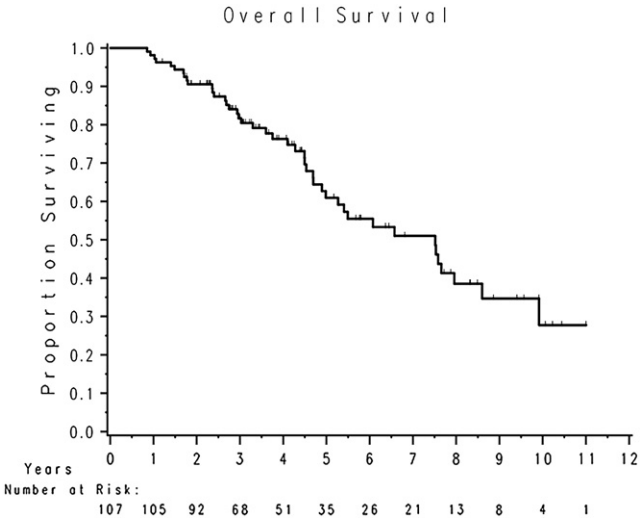

Fig. 2. Overall survival: at 3 years, 82%; at 5 years, 61%.

In total, 12 patients developed LRR, defined as pathologically confirmed recurrences in the ipsilateral CW and/or regional lymph nodes either during, or after the completion of radiation. Seven patients had failures isolated to the skin or CW, and 4 patients had regional nodal failures (1 supraclavicular, 1 axilla, 2 IMNs). One patient had experienced failure in both the CW and ipsilateral supraclavicular nodal region.

Unadjusted hazard ratios for the impact of clinical and treatment characteristics on LRR are shown in Table 4. As there were only 12 locoregional failures recorded, a multivariate analysis was not performed. Number of positive axillary lymph nodes and pathologic nodal ratio (NR) greater than 0.5 were significant variables ($p < 0.05$). Kaplan-Meier analysis of LRR-free survival according to NR is shown in Fig. 6. A value of NR > 0.5 was also predictive of distant metastases–free survival (DMFS) (Fig. 7, $p < 0.05$), but not OS ($p > 0.05$).

Preoperative taxanes use was associated with a lower likelihood of NR > 0.5. Of the 61 patients who received taxane

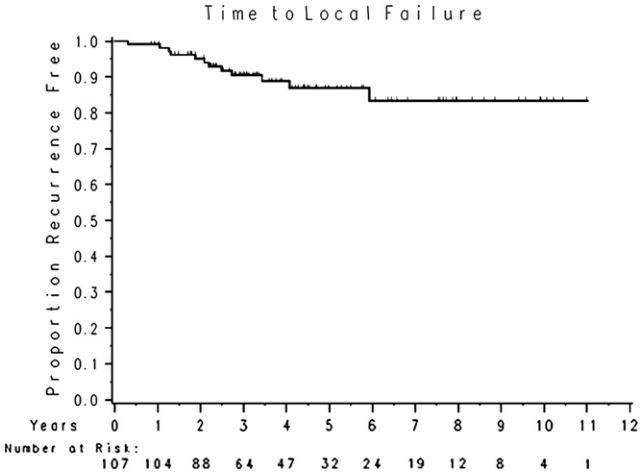

Fig. 3. Local recurrence–free survival: at 3 years, 90%; at 5 years, 87%.

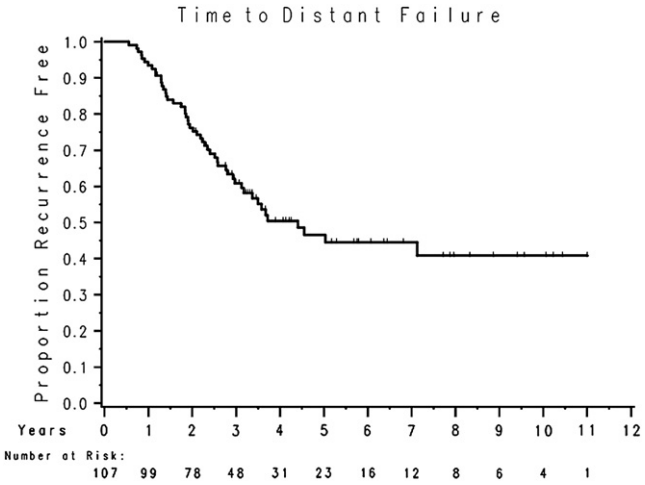

Fig. 4. Distant metastases–free survival: at 3 years, 61%; at 5 years, 47%.

before mastectomy, 16 (26%) had an NR > 0.5 vs. 21 (46%) of the 46 patients who did not receive preoperative taxanes ($p < 0.05$). Despite this finding, preoperative taxane use was not a significant predictor for LRR, as shown in Table 4.

No patient who received dose-dense chemotherapy or a scar boost experienced LRR. Therefore, hazard ratios were not calculated for these factors. The use of dose-dense chemotherapy did not significantly affect DMFS or OS.

Toxicity

All patients developed acute dermatitis (88% experienced a Grade 2 or higher skin reaction). Of the patients, 68% developed moist desquamation (Grade 2–3) during RT. Bolus on the skin was maintained throughout treatment as tolerable. Treatment breaks were discouraged but necessary in some circumstances because of skin toxicity.

Eleven patients received less than prescription dose to the CW secondary to intolerable moist desquamation. In this group, the median dose to the CW was 4,800 cGy (range, 3,800–4,980 cGy), with only 1 patient receiving less than

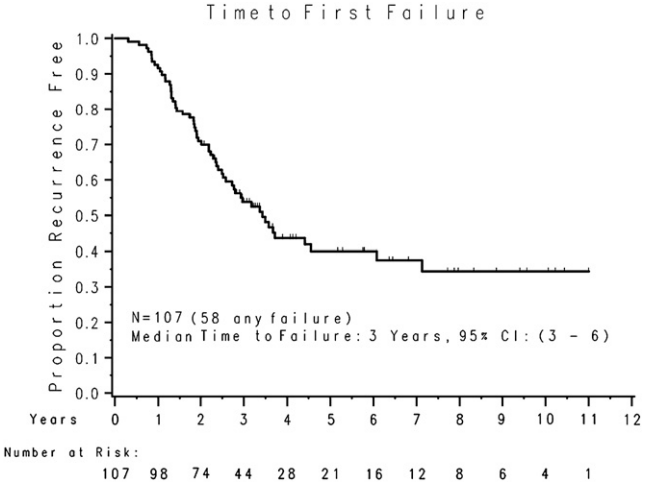

Fig. 5. Disease-free survival: At 3 years, 54%; at 5 years, 40%.

Table 4. Unadjusted analysis of time to local failure among study patients

Characteristic	Hazard ratio (95% CI)	*p* Value
Menopausal status		
Post	Ref	NS
Pre	0.81 (0.26–2.6)	
Margin status		
Positive	Ref	NS
Negative	0.38 (0.10–1.4)	
Clinical N-stage*		
IIIB	Ref	NS
IIIC	1.52 (0.20–11.9)	
Nodes positive		
0	Ref	NS
1–3	1.1 (0.04–17.2)	
4–9	2.6 (0.29–23.1)	
≥10	5.1 (0.61–42.1)	
>50% Nodes positive		
No	Ref	0.04
Yes	3.5 (1.05–11.6)	
Nodes positive (continuous)	11.4 (1.9–67.8)	0.008
Fraction size		
180	Ref	NS
200	0.28 (0.04–2.2)	
Electrons/photons		
Electrons only	Ref	NS
Photons	1.12 (0.36–3.5)	
Duration of RT		
≤39 Days	Ref	NS
>39 Days	1.26 (0.40–4.0)	
Time from surgery to RT		
≤6 Months	Ref	NS
>6 Months	2.54 (0.76–8.5)	
Response to neoadjuvant chemo†		
ALN pCR		
No	Ref	NS
Yes	0.79 (0.10–6.2)	
Breast pCR		
No	Ref	NS
Yes	0.32 (0.04–2.5)	
Preoperative taxane‡		
Yes	Ref	NS
No	0.90 (0.28–2.9)	

Abbreviations: Chemo = chemotherapy; CI = confidence interval; pCR = pathologic complete response; NS = not significant; RT = radiation therapy.

* Excludes the 6 patients who were Stage NX.

† Taken from date of surgery, after response to chemotherapy was assessed, includes only those patients who received neoadjuvant chemotherapy ($n = 101$).

‡ Excludes 5 patients who received surgery first and 5 patients who did not receive taxane.

4,600 cGy. Thirteen patients received less than the prescription dose to the regional lymph nodes because of acute toxicity with a median dose of 4,680 cGy to the supraclavicular region (range, 4,500–4,980 cGy). Altogether, 90 patients (84%) completed treatment to full dose as prescribed. Of note, no patient who stopped treatment early because of skin toxicity developed LRR. In all cases, the skin was noted to have healed in subsequent follow-up visits.

Late toxicities were documented at least 90 days after radiation using the Common Terminology Criteria for Adverse

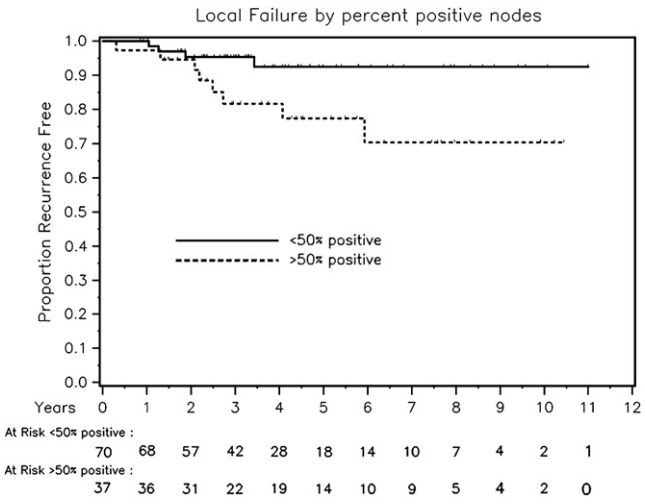

Fig. 6. Impact of nodal ratio (NR) on locoregional control (LRC).

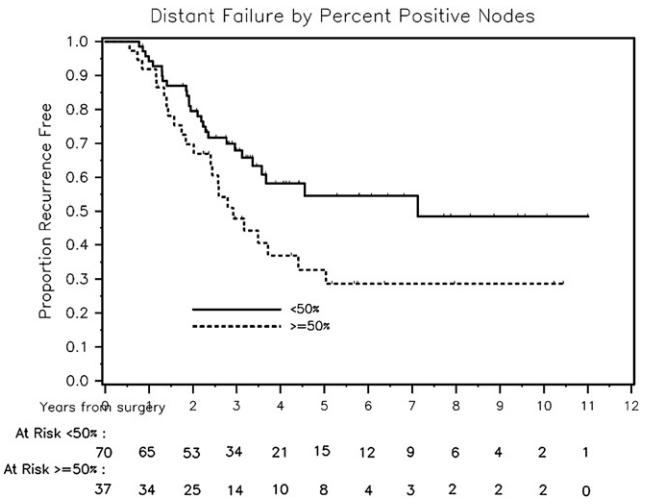

Fig. 7. Impact of nodal ratio (NR) on distant metastases–free survival (DMFS).

Events (CTCAE v3.0). Two patients developed Grade 4 skin toxicity; one developed ulceration on the mastectomy scar (attributed to a recall reaction from taxol), and the other developed radionecrosis of CW tissues after repeat RT for CW recurrence. One patient developed radiation pneumonitis requiring steroids. A total of 33 patients (31%) had documented lymphedema, resulting either from MRM, RT, or a combination of the two modalities. Only 2 patients had edema of the limb with >30% interlimb discrepancy (Grade 3). Subsequent malignancies, including 2 cases of contralateral IBC, occurred in 13 patients.

DISCUSSION

As the incidence of IBC continues to increase (18), the importance of optimizing both systemic and local therapies has become paramount. In locally advanced breast cancers, LRR is a devastating outcome, not only for its negative impact on quality of life (24) but also for its potential contribution to distant failures and death (25). We examined locoregional outcomes in a large population of IBC patients who received standard fractionation RT with daily skin bolus to 50 Gy in conjunction with contemporary CMT.

We found that this radiation regimen was effective and generally well tolerated, and that locoregional control (LRC) at 5 years (87%) was excellent. The disease-free survival and OS rates were comparable to those reported in other recent studies (26, 27). Caution must be used in applying these data to all IBC patients; however, as we excluded patients with metastatic disease or recurrent disease before RT. By applying these specific selection criteria, we sought both to study a homogenous population to provide clinically meaningful and applicable data and to facilitate comparison of our results with those of other published studies.

The largest recently published series on IBC comes from the MD Andersen Cancer Center (MDACC), where IBC patients have been treated with accelerated hyperfractionated (twice daily) treatment and with dose escalation (66 Gy) (19, 22). In the most recent MDACC update, Bristol *et al.* reported 84% LRC at 5 years in patients who completed CMT (22). The rationale for the use of altered fractionation is to reduce tumor repopulation and late effects (28). From a logistical point of view, however, a twice daily schedule is not practical for patients who travel considerable distances to receive radiation treatment, and it requires extra resources in busy radiation centers. Moreover, the superiority of accelerated fractionation for IBC has not been established and is unlikely to be studied in a randomized trial setting, given the rarity of IBC. In the same update, the authors found an association between dose escalation and increased risk of late toxicity including symptomatic lymphedema, brachial plexopathy, and CW fibrosis. The authors of this study concluded that dose escalation may not benefit all IBC patients who respond to NA chemotherapy and should be reserved only for patients with specific high-risk features (22).

Our study suggests that standard fractionation radiation with daily skin bolus is a reasonable and effective treatment regimen that may be a substitute to altered fractionation approaches in certain IBC populations. The locoregional outcomes we demonstrated were excellent and corroborated the results reported in the recent MDACC study, as well as other published studies that used a median dose of 50 to 60 Gy with daily fractionation for IBC and demonstrated 5-year LRC rates ranging from 78% to 92% (20, 21, 24, 29, 30). Our radiation technique differed from those described in previous studies in several important ways: (*1*) mastectomy scar boost was not routinely advocated, and performed in only a small fraction (11%) of patients (*2*) skin bolus was used daily to ensure that the entire surface of the skin was included within the prescription isodose line; and (*3*) the CW was most often treated with electron therapy to minimize the radiation dose to critical normal structures such as heart and lung.

Nodal status was the one prognostic variable examined that had a statistically significant impact on LRR. The risk for LRR appeared to increase with each additional involved lymph node and was significantly higher in patients with >50% axillary lymph node involvement at the time of

mastectomy. The finding that nodal status and nodal ratios may be an important predictor of local and distant recurrence in patients treated with NA chemotherapy agrees with recent literature (31, 32). The substantial proportion (35%) of our IBC cohort with NR > 0.5, even after primary chemotherapy, highlights the need for improved up-front systemic therapies targeted for this population.

The majority (95%) of our population received taxanes in addition to anthracycline-based chemotherapy. We found that preoperative taxane use was less likely to be associated with the negative predictor of NR > 0.5. Dose-dense therapy may be beneficial in IBC given the high proliferative nature of the cancer. A dose-dense regimen of epirubicin and docetaxel in a recently published Phase II trial for IBC demonstrated high response rates (15). Interestingly, in our study, no patient who received dose-dense AC-T chemotherapy had LRR. Despite this favorable effect, we were not able to demonstrate a statistically significant impact of dose-dense AC-T chemotherapy on DMFS or OS. Analysis of these data is limited, however, because of the retrospective nature of this study, in which assignment to dose-dense chemotherapy may have been confounded by other variables.

This study had several limitations. It was a single-armed retrospective review, and lacked a treatment comparison group. There were only few locoregional events, thereby making it difficult to demonstrate many predictors. The exclusion of all patients who had disease progression before RT limits the applicability of our study to all IBC patients, as nearly 25% present initially with distant metastases. The median follow-up for the group was only 4 years, which is reasonable, given the overall poor prognosis of the population. Nevertheless, longer follow-up would be helpful in assessing patient outcomes.

CONCLUSION

Standard fractionation radiation to 50 Gy with comprehensive nodal radiation and daily skin bolus was an effective and tolerable regimen for patients with IBC who received CMT including taxanes. Locoregional outcomes in our cohort of patients treated with this technique were excellent. Given the high rate of distant metastases and the aggressive behavior of this disease, further study of systemic agents is warranted.

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